STANFORD UNIVERSITY

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Ms. Kate-Louise Gottfried, J.D., M.S.P.H.
Executive Director
Office for Human Research Protections
Office of Public Health and Science, OS
6100 Executive Boulevard, Room 3B01 (MSC 7507)
Rockville, Maryland 20892-7507

Dear Ms. Gottfried:

Stanford University appreciates the opportunity to comment on the Office for Human Research Protections (OHRP) Draft Interim Guidance on Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection.

As a member of the scientific community, Stanford University is committed to the ethical pursuit of knowledge necessary for the development of new treatments and cures. In its pursuit, Stanford is committed to the protection of the rights and welfare of all individuals who volunteer to participate in research involving human subjects. We agree strongly with OHRP's principle that human subjects involved in research must not be placed at risk through the financial interest of clinical researchers or the institutions that conduct research.

The preservation of scientific integrity and the control of conflicts of interest are critically important to academic research. To achieve these ends, long-standing processes at Stanford University include an annual disclosure of outside interests by every faculty member, and the review of that information by School Deans in the context of the faculty member's range of academic responsibilities. Our policies and processes in this regard are both complex and thorough, as the issues involved are both broad and challenging. They comply fully with agency requirements, including those of the Department of Health and Human Services (DHHS).

At the same time, Institutional Review Boards (IRBs) at Stanford, as well as at other academic institutions, work to assure maximum protection for human subjects involved in any research activity. Our process in this regard relies on experts both inside and outside of Stanford University to evaluate the methodology and conduct of proposed studies.

These two processes — the administrative review of faculty members' outside financial interests, and the technical review of proposed research involving human subjects — are distinct but overlapping. Stanford University believes that the way in which it integrates these two is one example of how an institution can create and implement an effective system of controls unique to its size, organization and environment.

The draft guidance issued by OHRP suggests that institutions should flow financial disclosures through their IRBs and incorporate such disclosures onto consent forms. We believe it is essential for both IRBs and subjects to be informed on issues that might inhibit a researcher's objectivity. However, we believe it is problematic and potentially counterproductive to assume that IRBs can be the focal point for this activity.

Stanford, like other research universities, is working at the highest institutional levels to preserve academic integrity while allowing its faculty to explore appropriate avenues for research support. This institutional balance needs to inform all institutional actions, including those of the IRBs. To place the responsibility for review of conflicts of interest with IRBs would both overburden IRBs and underserve the academic community, including patients and research subjects.

We believe that the appropriate way for institutions to address conflicts of interest is in accordance with their own local procedures and policies. We believe that it is inappropriate for OHRP to create policy through "Interim Guidance," which as written currently, extends well beyond ordinary guidance or assistance. To this end we concur with the Association of American Universities (AAU), the Council on Governmental Relations (COGR), and the National Association of State Universities and Land-Grant Colleges (NASULGC) that OHRP should withdraw the current guidance and that HHS should reissue portions of the guidance as "points for consideration." We believe that this suggested course of action would supplement ongoing efforts on this issue by leaders in the academic and research communities and would allow for a more thoughtful deliberation on this issue and on any policy changes that may result.

We offer the following comments on the OHRP Guidance document for your review and consideration.

Section 1. <u>The Institution: Institutional Considerations</u>

Section (1.1) — The first guidance point assumes that every institution has one Conflict of Interest Committee that should share all aspects of its dealings and deliberations with the Institutional Review Board (IRB). We believe the decision to determine what mechanisms to employ to deal with conflict of interest matters and what information to share with an IRB is fundamentally a local decision best left to the discretion of individual institutions.

Section (1.3) — OHRP seems to imply that local affiliated IRB members are conflicted by the very nature of their institutional appointment and may not be free to operate in an autonomous manner without undesirable institutional pressures. Stanford believes this observation is unfounded, and although Stanford highly values its outside members, it does not believe that the "most effective means of protecting the integrity of the IRB process" is to have "broad participation of members from outside the institution." This action would require a revision to the IRB membership requirements (45 CFR 46.107), which wisely call for members with "varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution."

Section (1.4) — All institutions in compliance with the DHHS 1995 Conflict of Interest Policy collect and review annual financial disclosure information from all faculty. Extending this requirement for collection of financial information from non-faculty members of the IRB, *e.g*., unaffiliated members and IRB staff, seems unnecessarily burdensome. Instead, a policy statement in the Charge to the IRB could inform all IRB members of their obligation to abstain or recuse themselves from reviewing and approving studies when the member has a conflict of interest.

Section (1.6) — Stanford agrees with OHRP that institutions should not lose sight of the need to manage their own institutional conflicts of interest, but this duty should not be the responsibility of the IRB. This section also implies that, when institutional conflicts do exist, the well-being of the research participants may be best protected by having the clinical trial performed and evaluated by independent investigators at sites that do not have a financial investment in the outcome of a trial. OHRP should consider that the well-being of subjects may be best protected by having the trial performed and evaluated by individuals who know the most about a new device or an unusual disease and not necessarily by independent investigators at other sites, as this guidance implies.

Section (1.8) — This entire section places an inordinate and inappropriate amount of responsibility on the IRB to deal with looming complex matters of institutional conflict of interest. The general consensus of OHRP and most human subjects organizations and agencies is that IRBs are already overwhelmed with work. The task of ensuring that protocols involving human subjects are based upon acceptable medical risks and benefits for participants is challenging and requires many hours of careful review and discussion. At the August 2000 DHHS Conflict of Interest meeting, there were numerous warnings not to further burden IRBs. Creating new duties for IRBs related to conflict of interest oversight and management would

most certainly add substantially to the tremendous workload IRBs deal with currently.

IRBs should not be expected to adjudicate such issues as institutional equity interest, equity ownership, percentage of ownership of patents, royalties, and whether or not the institution stands to gain financially from a clinical trial. These issues extend well beyond the expertise and scope of IRB members. Ensuring accountability for these matters is the duty of the officers of the institution who have direct fiduciary responsibilities.

Section 2. Clinical Investigators

Any guidance that is developed by OHRP should be based on the premise that investigators will conduct ethically designed human clinical trials, and that these investigations will have the additional benefit of institutional oversight, monitoring, and accountability. Stanford University already requires disclosures by its faculty beyond even that envisioned by this suggested guidance. We fully agree that clinical investigators need to be sensitive to issues about scientific objectivity, and we have, and will continue to provide training and information in this regard. Holding individuals and institutions responsible for implementing processes that assure evaluation of conflicts locally and for documenting that these processes are followed is better than asking for written guidelines that oversimplify in the attempt to anticipate all possible circumstances.

Section 3. IRB Members and Staff

IRB members and Chairs can abstain or recuse themselves from deliberating and voting on protocols for a variety of reasons, and they do so frequently. As a matter of standard practice, Stanford reminds its IRB members regularly of their obligation to abstain or recuse themselves from reviewing, deliberating, and voting on protocols whenever they have any conflict of interest.

The first and last sentences of Section 3.1 incorporate conflicting language; first prescribing what the IRB chair should do, and then describing what many IRBs do in practice. As a guidance document, language that suggests, rather that prescribes, is preferable.

Section 4. IRB Review of Protocols and Approval of Consent Documents

Section (4.1) — This section places the management of the institution's financial relationships with research sponsors in the hands of the IRB. As previously mentioned in our response to Section (1.8), this is the wrong place for discussions of this nature to occur. IRBs are neither designed nor equipped to perform these functions, *e.g.,* to determine if a trial should be permitted to be carried out at the institution, to consider all categories in the DHHS Financial Conflict of Interest regulations, and to essentially take on the role of the Institutional Conflict of Interest Official. An IRB must have access to and communication with institutional officials charged with the overall management of conflict of interest matters but cannot be expected to perform their role.

Section (4.3) — Stanford agrees that the IRB application form should facilitate the collection of conflict of interest information from investigators, and Stanford has required this information from all investigators since the early 1980s. As an example of what a large institution has put in place, Stanford's process has evolved so that when a potential conflict of interest situation is disclosed to the IRB, the Principal Investigator is requested to refer the matter to his/her Department Chair and to the appropriate Senior Associate School Dean, who is the conflict of interest officer for the school. The conflict of interest officer then determines if the potential conflict should be managed, *e.g.*, with an oversight committee; mitigated, *e.g.*, by requiring a data safety monitoring board; or eliminated, *e.g.*, by moving the trial to another site. A process has been developed whereby there is communication between the conflict of interest officer, the IRB staff, and the IRB Chair (usually through the IRB staff) during this process. The conflict of interest officer, not the IRB, makes the decisions of how a potential conflict is to be handled and informs the IRB. The IRB then decides whether conflict of interest language should be included in the informed consent document. If the IRB determines conflict of interest language is needed, the IRB then decides what language will be required.

Section (4.4) — This section is intrusive into the institution's local policies and procedures. OHRP has predetermined that Clinical Investigators, who have a financial conflict of interest, should not be approved by the institution's IRB to be directly engaged in certain aspects of a trial, *e.g.,* the design, monitoring, obtaining informed consent, adverse event reporting, or analyzing data. In many environments, including Stanford, these decisions are better made and managed by a conflict of interest committee in consultation with the institution's conflict of interest officers and the IRB.

Section 5. Consent

The written consent document has become very long and complicated over the years as a result of well-meaning, additive regulation and guidance. The addition of such information as funding arrangements, how a potential conflict is being managed, and what additional "protections" have been put in place to protect subjects from a potential conflict of interest that could confuse or distract subjects in regards to the basic medical risks and the benefits of a study. Stanford believes that the OHRP guidance in this section is too prescriptive and could lead to unintended consequences such as subject confusion or information overload. The specific language about conflict of interest required in the consent form is best decided by the local bodies charged with protecting human subjects and will be dependent upon many different factors. For example, Stanford has routinely included information about the source of funding for clinical trials in the consent form for many years.

The implication that non-biased third parties are readily available to obtain consent is not correct when the protocol concerns complex diseases and interventions. Specific expertise is often required to explain risks and benefits and alternatives to human subjects. The consent process is most likely to be managed effectively when based on locally defined requirements designed to address issues that arise in the specific circumstance.

During the past several years, IRBs have been inundated with voluminous new regulations, policies, interpretations of existing policies, best practices, position statements, guidance, and now "interim guidance." Often, the contents of these documents are in conflict with existing policies, practices, and procedures. Our common and primary goal, to enhance the protection of human subjects, has not always been well served or furthered by these prolific and conflicting regulatory actions.

In summary, OHRP should offer general approaches, rather than specific, detailed directions to IRBs and institutions. OHRP could provide valuable resource materials incorporating examples of how various situations might be handled. Our common objective of achieving consistent and careful practices for protection of human subjects would benefit from an educational focus in which examples and paradigms for management are elaborated and made available for training activities at institutions around the United States.

Instead, the OHRP Guidance document now reads more like a policy document, and as such, would be in conflict with existing DHHS policy on conflict of interest and commitment. We recommend that OHRP withdraw its "Interim Guidance" until DHHS can

formally address this matter to assure consistency with existing policies and to allow more time and opportunity for thoughtful input from all parties interested in the protection of human research subjects.

Thank you for the opportunity to comment on this Guidance document.

Sincerely,

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